



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/016,505	12/10/2001	Peter W. Laird	47675-9	8355

22504 7590 10/28/2004

DAVIS WRIGHT TREMAINE, LLP  
2600 CENTURY SQUARE  
1501 FOURTH AVENUE  
SEATTLE, WA 98101-1688

EXAMINER
----------

GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
----------	--------------

1634

DATE MAILED: 10/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 10/016,505	<b>Applicant(s)</b> LAIRD ET AL.	
	<b>Examiner</b> Jeanine A Goldberg	<b>Art Unit</b> 1634	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 13 August 2004.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 27-36,38-47,49-59 and 61-68 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 27-36,38-47,49-59 and 61-68 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>7/04</u> . | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

1. This action is in response to the papers filed August 13, 2004. Currently, claims 27-36, 38-47, 49-59, 61-68 are pending.
2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 13, 2004 has been entered.
3. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.
4. Any objections and rejections not reiterated below are hereby withdrawn.

### ***New Matter***

5. Claims 33, 35, 44, 46, 56, 58, 67 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, reference to "a molecular beacon-type probe," and "a dual-label hydrolysis probe" are included. The amendment proposes that the new claim language is supported on page 8, 15 and 16 of the specification. However, the

Art Unit: 1634

specification does not describe or discuss "a molecular beacon-type probe," and "a dual-label hydrolysis probe." Instead the specification describes dual probe technology, fluorescent primers, and fluorescence based quantitative PCR. This description does not support "a molecular beacon-type probe," and "a dual-label hydrolysis probe". The concept of "a molecular beacon-type probe," and "a dual-label hydrolysis probe" does not appear to be part of the originally filed invention. Therefore, "a molecular beacon-type probe," and "a dual-label hydrolysis probe" constitutes new matter. Applicant is required to cancel the new matter in the reply to this Office Action.

**Response to Arguments**

The response traverses the rejection. The response asserts that hydrolysis probes, and molecular beacons are art recognized Dual label FRET probes, and as recognized in the art at the time of filing. This argument has been reviewed but is not convincing because the description and new matter requirement requires that "a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." The test is not one of what was known in the art. Inventions are typically made up of combinations of known methods to form a new method. An invention is fixed at the time of filing and adding limitations which were not present at the time of filing is not permitted. At the time of filing, the instant specification appears to discuss dual labeled FRET probes. It is acknowledged that additional probes existed in the art, however, the instant specification does not appear to contemplate or describe these probes for use in the instant method. The disclosure of a particular species would not

Art Unit: 1634

describe a much broader genus. The response fails to provide any direct support found in the specification for molecular beacons, or a dual-label hydrolysis probes.

The response asserts that Whitcombe describes comparing scorpion primers against two examples of dual labeled probes; namely TaqMan and Molecular Beacon. This argument has been thoroughly reviewed, but is not found persuasive because Whitcombe is not discussed in the instant application nor incorporated by reference. The instant specification describes Lightcycler technology (which is energy transfer between two adjacent hybridizing probes) and Sunrise technology (fluorescence is generated by the primer itself (Page 15, lines 25-30)). The claims are drawn to a dual-label hydrolysis probe. The instant specification does not appear to specifically describe what a dual-label hydrolysis probe encompasses. The instant specification does not appear to contain the word hydrolysis. A search of the prior art and the patent literature does not appear to provide a description for a dual-label hydrolysis probe.

Both the specification and the art teaches that a molecular beacon is a hairpin like structure which is a short segment of single stranded DNA. The bases on either end of the probe are complementary to one strand of the PCR product. In contrast, the specification describes TaqMan probes, Sunrise and Lightcycler. None of these probes are hairpin structures or molecular beacons. Thus the specification fails to describe a method of using molecular beacon-type probes.

As stated above, it is unclear what is encompassed by dual-label hydrolysis probe since the specification fails to describe such a probe.

Thus for the reasons above and those already of record, the rejection is maintained.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 27-34, 36, 38-45, 47, 49-57, 59, 61-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herman et al (US Pat. 6,017,704, January 25, 2000) in view of Wittwer et al (US Pat. 6,140,054, October 2000).

Herman et al. (herein referred to as Herman) teaches a method of detection of methylated nucleic acids using agents which modify unmethylated cytosine and distinguishing modified methylated and non-methylated nucleic acids. Herman teaches

Art Unit: 1634

a method for detecting cytosine methylation and methylated CpG islands within genomic sample of DNA by contacting the sample of genomic DNA with bisulfite, amplifying the converted nucleic acid with primers which distinguish between unmethylated and methylated nucleic acids such that at least one oligonucleotide probe is a CpG specific probe and detecting the methylated nucleic acid based on an amplification mediated change or property thereof in relation to another probe or primer. Specifically Herman teaches using MSP primers that are specifically designed to recognize CpG sites to take advantage of the differences in methylation to amplify specific products to be identified (col. 5, lines 3-5). Herman teaches that the "only technique that can provide more direct analysis than MSP for most CpG sites within a defined region is genomic sequencing" (col. 5, lines 30-35). Herman teaches a method for detecting a methylated CpG containing nucleic acid by obtaining nucleic acid and treating the nucleic acid with an agent that modifies unmethylated cytosine (col. 5, lines 58-63). The agent is preferably sodium bisulfite which modifies unmethylated cytosine, but not methylated cytosine (col. 6, lines 9-13)(limitations of Claim 29-30). Moreover, amplification is carried out using primers specific for CpG-specific oligonucleotides such that the primer distinguish between modified methylated and non-methylated nucleic acids and finally detecting the methylated nucleic acids (col. 5, lines 60-67). Herman teaches that treatment with sodium bisulfite modifies unmethylated cytosine. This allows the allele specific detection of methylated nucleotides. Herman teaches that the amplified products are preferably identified as methylated or non-methylated by sequencing (col. 9, lines 51-55). Among the sequencing methods suggested by

Art Unit: 1634

Herman, allele-specific oligonucleotide probe analysis is listed (col. 9, lines 55-65).

Allele-specific oligonucleotide (ASO) probes are specific probes which allow differentiation between different sequences. ASO probe detection is among the list of means for sequencing the amplified products to identify methylated or non-methylated sequences.

Herman does not specifically teach using a FRET probe to detect allele specific differences in genomic DNA which have been treated with bisulfite to analyze methylation status of the nucleic acid.

However, Wittwer et al. (herein referred to as Wittwer) teaches a method of using FRET probes to detect polymorphisms. Wittwer teaches that the methods of ASO hybridization require time consuming multiple manual steps. Therefore, Wittwer uses melting temperatures of fluorescent hybridization probes that hybridize to a PCR amplified region to identify polymorphisms (col. 1, lines 30-35). Wittwer teaches that in a preferred embodiment the hybridization probe comprises two oligonucleotide probes that hybridize to adjacent regions of a DNA sequence wherein each oligonucleotide probe is labeled with a respective member of a FRET pair (col. 2, lines 45-50). The presence of the target nucleic acid sequence in a biological sample is detected by measuring fluorescent energy transfer between the two labeled oligonucleotides (col. 2, lines 45-50). Wittwer teaches in combination with standard melting curve analysis, single point mutations in a gene can be distinguished from the normal gene (col. 3, lines 20-25). Wittwer also teaches that one of the labeled oligonucleotides also functions as a PCR primer ("probe-primer"), then the two fluorescently labeled oligonucleotides

Art Unit: 1634

hybridize to opposite strands of a DNA sequence (col. 3, lines 40-45)(limitations of Claim 36). Wittwer teaches designing oligonucleotide probes identical in sequence to the complementary wild type sequence which will dissociate from the locus containing a mutation at a lower temperature than it will from the wild type locus (col. 4, lines 5-15). The probes of Wittwer contain fluorescent labeled dyes that when in close proximity the resonance energy transfer is high (col. 9, lines 7-10). The probes may comprise multiple sets of FRET oligonucleotide pairs which can be labeled with different fluorescent resonance energy transfer pairs (col. 12, lines 55-65). The method allows for a rapid procedure that can be conducted within a single reaction vessel for detecting polymorphisms in genomic DNA samples (col. 7, lines 15-25). Specifically Wittwer teaches that the method comprises the steps of combining a biological sample comprising nucleic acid sequences with a pair of oligonucleotide PCR primers and two or more FRET oligonucleotide pairs, adding a thermostable polymerase, amplifying a selected segment of the nucleic acid sequence by the polymerase chain reaction and illuminating the biological sample and monitoring the fluorescence as a function of temperature (col. 7, lines 20-30).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified and improved the method of Herman which detected allele specific differences in genomic DNA following bisulfite treatment using ASO probes with the allele specific detection method of Wittwer. Herman specifically teaches treating the nucleic acid with bisulfite prior to amplification and detection. Since the genomic nucleic acid has been treated to convert un-methylated

Art Unit: 1634

nucleic acids, the sequence differs between the methylated and unmethylated nucleic acids. Herman teaches that ASO probes are a means of sequencing to determine whether the nucleic acid is identified as methylated or non-methylated (col. 9, lines 50-60). The ordinary artisan would have recognized based upon the teachings of Wittwer that ASO hybridization require time consuming multiple manual steps and would have been motivated to have modified the method to encompass a more efficient method of detection. Wittwer specifically teaches the method of using FRET probes to detect the presence of alleles or polymorphisms is less time consuming and require less manual steps. Moreover, Wittwer's method allows detection in a single reaction vessel. Therefore, the ordinary artisan would have been motivated to have detected allele specific differences in bisulfite treated DNA using FRET probes for the specific benefits taught by Wittwer.

With respect to Claim 38-45, 47, 49, the claims specifically require that the primer do not distinguish between modified and unmethylated and methylated nucleic acids. Herman specifically states that amplified products may be identified as methylated or non-methylated by sequencing such as by allele-specific oligonucleotides. Thus, it would follow that any amplified product whether or not the nucleic acid was first amplified with primers which distinguished between modified unmethylated and methylated nucleic acids would allow detection by allele specific oligonucleotides. Without using primers that are methylation specific would provide greater versatility to the assay and would allow obtaining an amplicon which was either methylated or unmethylated. Given the teachings in Herman that nucleic acids may be identified as

Art Unit: 1634

methyated or non-methyated by sequencing, the ordinary artisan would have been motivated to have detected methylation status within these sequences by FRET probes which were taught in the art to be preferable to ASO probes taught in Herman. The ordinary artisan would have been motivated to have detected the allele differences using FRET probes during amplification for the reasons specifically articulated in Wittwer.

### **Response to Arguments**

The response explains the instant invention and the method of Herman. The response asserts that Herman does not disclose or suggest CpG-specific oligonucleotide probes. This argument has been reviewed but is not convincing because following bisulfite treatment, the nucleotide sequence within a CpG island is differentially altered between methyated regions and non-methyated regions. Herman specifically teaches that the amplified products may be identified as methyated or non-methyated by sequencing such as ASO probes. ASO probes may detect the differences C and T in methyated vs unmethyated nucleic acids.

The response argues that the method of Whittwer is only a quasi real-time method. This argument has been thoroughly reviewed, but is not found persuasive because the instant claims are drawn to detecting, during the amplification the methyated nucleic acid based on at least one of amplification-mediated probe displacement and amplification-mediated change of probe fluorescence. The method of Whittwer states that the continuous monitoring of fluorescence during the PCR reactions provides a system for detecting sequence alterations internal to the PCR

Art Unit: 1634

primers by resonance energy transfer and probe melting curves (col. 16, lines 5-10).

Moreover, the claims do not particularly require real-time methods, but rather a method of detecting during the amplification. Thus, while it appears that Whittwer teaches a real time method the claims are not limited to such a method.

The response asserts that the instant method does not require determination of melting curves as the claimed methods of Whittwer. This argument has been thoroughly reviewed, but is not found persuasive because the claims do not particularly exclude such a limitation. The instant claims are openly and broadly drawn to a method of detecting, during the amplification the methylated nucleic acid based on at least one of amplification-mediated probe displacement and amplification-mediated change of probe fluorescence.

Thus for the reasons above and those already of record, the rejection is maintained.

8. Claims 27-35, 38-46, 49-58, 61-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herman et al (US Pat. 6,017,704, January 25, 2000) in view of Whitcombe et al (US Pat. 6,270,967, August 2001).

Herman et al. (herein referred to as Herman) teaches a method of detection of methylated nucleic acids using agents which modify unmethylated cytosine and distinguishing modified methylated and non-methylated nucleic acids. Herman teaches a method for detecting cytosine methylation and methylated CpG islands within genomic sample of DNA by contacting the sample of genomic DNA with bisulfite,

Art Unit: 1634

amplifying the converted nucleic acid with primers which distinguish between unmethylated and methylated nucleic acids such that at least one oligonucleotide probe is a CpG specific probe and detecting the methylated nucleic acid based on an amplification mediated change or property thereof in relation to another probe or primer. Specifically Herman teaches using MSP primers that are specifically designed to recognize CpG sites to take advantage of the differences in methylation to amplify specific products to be identified (col. 5, lines 3-5). Herman teaches that the "only technique that can provide more direct analysis than MSP for most CpG sites within a defined region is genomic sequencing" (col. 5, lines 30-35). Herman teaches a method for detecting a methylated CpG containing nucleic acid by obtaining nucleic acid and treating the nucleic acid with an agent that modifies unmethylated cytosine (col. 5, lines 58-63). The agent is preferably sodium bisulfite which modifies unmethylated cytosine, but not methylated cytosine (col. 6, lines 9-13)(limitations of Claim 29-30). Moreover, amplification is carried out using primers specific for CpG-specific oligonucleotides such that the primer distinguish between modified methylated and non-methylated nucleic acids and finally detecting the methylated nucleic acids (col. 5, lines 60-67). Herman teaches that the amplified products are preferably identified as methylated or non-methylated by sequencing (col. 9, lines 51-55). Among the sequencing methods suggested by Herman, allele-specific oligonucleotide probe analysis is listed (col. 9, lines 55-65). Allele-specific oligonucleotide (ASO) probes are specific probes which allow differentiation between different sequences.

Herman does not specifically teach using a TaqMan probe to detect allele specific differences in genomic DNA which have been treated with bisulfite to analyze methylation status of the nucleic acid.

However, Whitcombe illustrates the use of a TaqMan probe (xyz) for allele discrimination of the ASO element (Figure 10, col. 8, lines 58-62). Whitcombe teaches that when using TaqMan for allele discrimination the ASO element of the approach requires that the probe annealing is borderline to obtain maximum differentiation between the variants. Whitcombe teaches that the use of TaqMan probe allows realtime or end point detection of the released fluorophore. As seen in Figure 11, Whitcombe teaches a method of using molecular beacons which make use of a similar quenching effect (col. 8, lines 65-68).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified an improved the method of Herman which detected allele specific differences in genomic DNA following bisulfite treatment using ASO probes with the allele specific detection method for detection of allele specific detection using a TaqMan probe as suggested by Whitcombe. Herman specifically teaches treating the nucleic acid with bisulfite prior to amplification and detection. Since the genomic nucleic acid has been treated to convert un-methylated nucleic acids, the sequence differs between the methylated and unmethylated nucleic acids. Herman teaches that ASO probes are a means of sequencing to determine whether the nucleic acid is identified as methylated or non-methylated (col. 9, lines 50-60). Whitcombe specifically teaches using a TaqMan probe in the ASO detection of an

Art Unit: 1634

allele. Therefore, the ordinary artisan would have recognized that using a TaqMan probe as opposed to an ASO hybridization would have the expected benefits of realtime detection of the released fluorophore. Therefore, the ordinary artisan would have been motivated to have detected allele specific differences in bisulfite treated DNA using FRET probes for the specific benefits taught by Whitcombe.

With respect to Claim 38-46, 49, the claims specifically require that the primer do not distinguish between modified and unmethylated and methylated nucleic acids. Herman specifically states that amplified products may be identified as methylated or non-methylated by sequencing such as by allele-specific oligonucleotides. Thus, it would follow that any amplified product whether or not the nucleic acid was first amplified with primers which distinguished between modified unmethylated and methylated nucleic acids would allow detection by allele specific oligonucleotides. Without using primers that are methylation specific would provide greater versatility to the assay and would allow obtaining an amplicon which was either methylated or unmethylated. Given the teachings in Herman that nucleic acids may be identified as methylated or non-methylated by sequencing, the ordinary artisan would have been motivated to have detected methylation status within these sequences by FRET probes which were taught in the art to be preferable to ASO probes taught in Herman. The ordinary artisan would have been motivated to have detected the allele differences using Taqman or beacon probes during amplification for the reasons specifically articulated in Whitcombe.

### **Response to Arguments**

The response explains the instant invention and the method of Herman. The response asserts that Herman does not disclose or suggest CpG-specific oligonucleotide probes. This argument has been reviewed but is not convincing because following bisulfite treatment, the nucleotide sequence within a CpG island is differentially altered between methylated regions and non-methylated regions. Herman specifically teaches that the amplified products may be identified as methylated or non-methylated by sequencing such as ASO probes. ASO probes may detect the differences C and T in methylated vs unmethylated nucleic acids.

The response asserts that there is no suggestion in the art to combine a real-time allele discrimination method with a methylation assay that is dependent on methylation detection. This argument has been thoroughly reviewed, but is not found persuasive because Whitcombe and the art teach the benefits of performing a real-time assay. Real-time assays provide a continuous idea of the assay and its changes throughout PCR. Thus for the reasons above and those already of record, the rejection is maintained.

9. Claims 61-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herman et al (US Pat. 6,017,704, January 25, 2000).

Herman et al. (herein referred to as Herman) teaches a method of detection of methylated nucleic acids using agents which modify unmethylated cytosine and distinguishing modified methylated and non-methylated nucleic acids. Herman teaches a method for detecting cytosine methylation and methylated CpG islands within genomic sample of DNA by contacting the sample of genomic DNA with bisulfite,

amplifying the converted nucleic acid with primers which distinguish between unmethylated and methylated nucleic acids such that at least one oligonucleotide probe is a CpG specific probe and detecting the methylated nucleic acid based on an amplification mediated change or property thereof in relation to another probe or primer. Specifically Herman teaches using MSP primers that are specifically designed to recognize CpG sites to take advantage of the differences in methylation to amplify specific products to be identified (col. 5, lines 3-5). Herman teaches that the "only technique that can provide more direct analysis than MSP for most CpG sites within a defined region is genomic sequencing" (col. 5, lines 30-35). Herman teaches a method for detecting a methylated CpG containing nucleic acid by obtaining nucleic acid and treating the nucleic acid with an agent that modifies unmethylated cytosine (col. 5, lines 58-63). The agent is preferably sodium bisulfite which modifies unmethylated cytosine, but not methylated cytosine (col. 6, lines 9-13)(limitations of Claim 29-30). Moreover, amplification is carried out using primers specific for CpG-specific oligonucleotides such that the primer distinguish between modified methylated and non-methylated nucleic acids and finally detecting the methylated nucleic acids (col. 5, lines 60-67). Herman teaches that the amplified products are preferably identified as methylated or non-methylated by sequencing (col. 9, lines 51-55). Among the sequencing methods suggested by Herman, allele-specific oligonucleotide probe analysis is listed (col. 9, lines 55-65). Allele-specific oligonucleotide (ASO) probes are specific probes which allow differentiation between different sequences.

Herman teaches that the kit comprises a reagent that modified unmethylated cytosine nucleotides; primers for amplification of unmethylated CpG-containing nucleic acid; primers for the amplification of methylated CpG-containing nucleic acid; primers for the amplification of control nucleic acid (col. 18, lines 50-65).

Herman does not specifically teach packaging a probe necessary for the method into a kit.

However, the method of Herman specifically encompasses using a CpG specific probe for detection of the methylation status of the nucleic acid.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Herman to include an ASO probe in the kit. The ordinary artisan would have been motivated to have packaged the primers, ASO probes, and reagents of Herman into a kit for the purpose of saving time and money. The method of Herman specifically suggests that probes may be used to detect the methylation status of the nucleic acid. Thus, adding a probe which may detect the methylation status of the nucleic acid to the kit would have been obvious at the time the invention was made.

### **Response to Arguments**

The response traverses the rejection. The response asserts that the rejection is traversed on the basis of the previous rejections under Herman. This argument has been reviewed but is not convincing because the teachings of Herman do teach using a probe in combination with primers. The response suggests that Herman uses ASO probes post-amplification. The limitation within the newly added claim directed to how

to use the CpG-specific probe during amplification is not a structural limitation which would alter the composition of the claim. The claims to kits are directed to product claims, thus, the means in which the products are used is not essential to the kit claim. Thus for the reasons above and those already of record, the rejection is maintained.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 27-32, 38-43, 50-55, 61-67 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-26 of U.S. Patent No. 6,331,393 (December 18, 2001).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by or would have been obvious over, the reference claim(s). See e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentable distinct from each other because Claim 27-32, 38-43, 50-55, 61-67 of the instant application is generic to all that is recited in Claim 1-26 of U.S. Patent No. 6,331,393. That is, Claim 1-26 of 6,331,393 falls entirely within the scope of Claim 27-32, 38-43, 50-55, 61-67, or in other words, Claim 27-32, 38-43, 50-55, 61-67 is anticipated by Claim 1-26 of 6,331,393. Here, claim 27 recites a method for detecting cytosine methylation and methylated CpG islands by contacting a genomic sample of DNA with a modifying agent, amplifying the nucleic acid with primers and detecting the methylated nucleic acid based on an amplification-mediated, or amplification product-mediated change in a property of the CpG-specific probe or in a property thereof in relation to another probe or primer. The claims of U.S. Patent No. 6,331,393 are directed specifically to detecting the methylated nucleic acid based on amplification-mediated displacement of the CpG specific probe. Therefore, the specific detection means claimed falls within the scope of the broad genus of detection methods allowed in Claim 27, 38, 50. Moreover, the Claims drawn to the kits, namely Claim 61 of the instant application and Claim 20 of 6,331,393 differ only in the recitation of the probe which is based on amplification-mediated displacement. Therefore, the claims are not patentable distinct from one another.

### **Response to Arguments**

The response indicates that Applicants are fully prepared to timely file a Terminal Disclaimer upon notification of allowable subject matter. Thus for the reasons above and those already of record, the rejection is maintained.

**Conclusion**

**11. No claims allowable.**

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272- 0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



**Jeanine Goldberg**  
**Patent Examiner**  
October 26, 2004



**BRUCE KISLIUK, DIRECTOR**  
**TECHNOLOGY CENTER 1600**